AMENDED SPECIFICATION

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PATENT SPECIFICATION

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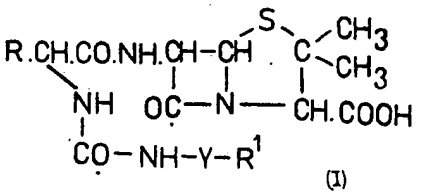
(72) Inventors KENNETH DAVID HARDY and GORDON RODNEY THOMAS

(54) PENICILLINS

(71) We, BEECHAM GROUP LIMITED, a British Company, of Beecham House, Great West Road, Brentford, Middlesex, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new penicillins and is particularly concerned with a new class of penicillins which are derivatives of 6-aminopenicillanic acid and which are of value as antibacterial agents, as nutritional supplements in animal food, as agents for the treatment of mastitis in cattle and as therapeutic agents in poultry and animals, including man, in the treatment especially of infectious diseases caused by Gram-positive and Gram-negative bacteria.

According to the present invention there are provided penicillins of the general formula:—



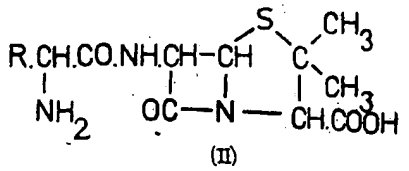
(I)

and non-toxic salts thereof, where R is a phenyl, substituted phenyl or thienyl group, R^1 is an alkyl, alkenyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, alkylthio, arylthio, aralkylthio or heterocyclic group which may be substituted and Y is SO_2.

The invention also provides penicillins of the general formula (I) and non-toxic salts thereof in which R is a phenyl or thienyl group, R′ is as defined above, but Y is the group CO.

The salts are non-toxic salts including non-toxic metallic salts such as sodium, potassium, calcium and aluminium, ammonium and substituted ammonium salts, e.g. salts of such non-toxic amines as trialkylamines, including triethylamine, procaine, dibenzylamine, N-benzyl-beta-phenethylamine 1 - ephenamine, N,N′ - dibenzylethylenediamine, dehydroabietylamine, N,N′ - bis - dehydroabietylethylenediamine, and other amines which have been used to form salts with benzylpenicillin.

The present invention further provides a process for the preparation of penicillins having the general formula (I) in which an α-aminopenicillin of the general formula:—



(II)

or a salt thereof is reacted in an organic solvent with an isocyanate or isothiocyanate of the general formula $R^1.Y.NCO$ where R^1 is as hereinbefore defined, and either (a) R is phenyl, substituted phenyl or thienyl and Y is SO_2; or (b) R is a phenyl or thienyl group and Y is CO.

The α-aminopenicillin (II) may be employed in either epimeric form or as the DL-mixture to produce the corresponding form

of the penicillin (I). When R is a phenyl group it is preferred to use D - α - aminobenzylpenicillin as the starting penicillin in order to give the most active products.

The following examples illustrate the invention:—

EXAMPLE 1.

D - α - (N - Benzoylureido)benzylpenicillin.

A suspension of anhydrous D - α - aminobenzylpenicillin (6.98 g., 0.02 mol.) in methylene chloride (75 ml) was cooled to 5°C., triethylamine (11 ml.) added, and the mixture stirred for 45 minutes at room temperature. The mixture was filtered and to the clear filtrate, cooled to 0°C, was added dropwise a solution of benzoyl isocyanate (2.9 g., 0.02 mol.) in methylene chloride (10 ml.). The mixture was stirred at 0°C for a further 2 hours, and the resulting clear solution was concentrated at low temperature and pressure. Water (100 ml.) was added followed by ethyl acetate (100 ml.) and the aqueous phase acidified to pH 2.0 with N/1 hydrochloric acid. The ethylacetate layer was separated and combined with further ethyl acetate extracts (2 × 100 ml.) of the aqueous layer. The combined organic extracts were washed with water (100 ml.) and saturated brine (150 ml.), and clarified by filtration through Celite ("Celite" is a Registtred Trade Mark). The solution was treated with 2N potassium - 2 - ethyl hexoate in isopropanol (10 ml.). The separated oil was triturated with dry ether and the resulting solid filtered, and dried *in vacuo*. This solid was digested in water (165 ml.), stirred vigorously and traces of undissolved material separated by decantation. The solution was acidified to pH 1.8 with N/1 hydrochloric acid, and the resulting precipitate filtered and washed with water. After drying *in vacuo* over phosphorous pentoxide, the solid was dissolved in ethyl acetate (200 ml.) and treated with 2N potassium-2-ethyl hexoate in isopropanol (10 ml.). The resulting oil was triturated with dry ether to give the penicillin potassium salt as a colourless solid in 51% weight yield.

The product was estimated to be 92% pure by colorimetric assay with hydroxylamine.

EXAMPLE 2.

D - α - (N - p - Methoxybenzoylureido)benzylpenicillin.

A solution of p-methoxybenzoyl isocyanate (1.77 g., 0.01 mol.) in methylene chloride (10 ml.) was added, with stirring and cooling, to a clear solution of anhydrous D-α- aminobenzylpenicillin (3.49 g., 0.01 mol.) in a mixture of methylene chloride (20 ml.) and triethylamine (3 ml.) at 0°C. The mixture was stirred at 0°C for 2 hours and filtered through Celite to clarify. The filtrate was extracted with water (2 × 20 ml.) and the aqueous extracts combined and washed with ether (20 ml.). The aqueous layer was covered with ethyl acetate (30 ml.) and acidified to pH 1.5 with N hydrochloric acid. The organic layer was separated and the aqueous layer re-extracted with ethyl acetate (2 × 30 ml.). The combined organic extracts were washed with water (10 ml.) and dried over magnesium sulphate. The dried ethylacetate solution was treated with a 1.67N solution of sodium 2-ethylhexoate in methylisobutyl ketone (6 ml.). The precipitated solid was filtered off, washed with dry ether and dried *in vacuo* to give the penicillin sodium salt 4.64 g. (84.7%) as a colourless non-crystalline solid.

EXAMPLE 3.

D - α - (N - p - Chlorobenzoylureido)benzylpenicillin.

A solution of p-chlorobenzoyl isocyanate (1.87 g. 0.01 mol.) in methylene chloride (10 ml.) was added, with stirring and cooling, to a clear solution of anhydrous D - α - aminobenzoylpenicillin (3.49 g., 0.01 mol.) in a mixture of methylene chloride (20 ml.) and triethylamine (3 ml.) at 0°C. The reaction mixture was stirred at 0°C. for 2 hours and worked up as described in Example 8 to give the penicillin sodium salt 3.44 (61.5%) as a colourless non-crystalline solid.

EXAMPLE 4.

The following penicillins of the general formula (I), R=phenyl; Y=CO were prepared as described as in Example 2 and isolated as their non-crystalline sodium salts:—

	R^1	Yield %
a	α-furyl	82.5
b	α-thienyl	81.6
c	β-thienyl	76.5
d	CH_3–	61.5
e	$(CH_3)_2CHCH_2$–	74.0
f	$CH_2CH_2CH_2$–	12.5
g	*o* $CH_3OC_6H_4$–	79.7
h	*m* $CH_3OC_6H_4$–	82.9
i	*p* $ClC_6H_4OCH_2$–	74.5
j	$C_6H_5CH_2$–	74.0
k	*p* BrC_6H_4–	73.7
l	CCl_3	86.2
m	$C_6H_5CH_2O$	81.5
n	*p* $NO_2C_6H_4$–	76.9
p	5-methylisoxazol-2-yl	86.0
q	C_2H_5O–	80.0
r	C_6H_5O–	83.0
s	*p* $(C_6H_5CH_2OOCNH)C_6H_4$–	74.6
t	*p* $(C_6H_5CH_2O)C_6H_4$–	63.1
u	*p* F C_6H_4–	74.7
v	2,6–$(CH_3O)_2C_6H_3$–	99.5

EXAMPLE 5.

D - α - (N - p - Cyanobenzoylureido)benzylpenicillin.

A solution of p-cyanobenzoyl isocyanate (4.3 g. 0.025 mol.) in methylene chloride (30 ml.) was added, with stirring and cooling, to a clear solution of anhydrous D - α - aminobenzoylpenicillin (8.73 g. 0.025 mol.) in a mixture of methylene chloride (50 ml.) and triethylamine (7.5 ml.) at 0°C. The reaction mixture was stirred at 0°C for 2 hours and evaporated under reduced temperature and pressure. The residue dissolved in water (250 ml.), was covered with ethyl acetate (*75 ml.*) and adjusted to pH 1.5 with N hydrochloric acid. The ethyl acetate layer was separated and the aqueous layer re-extracted with ethyl acetate (2 × 75 ml.). The penicillin free acid separated from the combined ethyl acetate extracts and was filtered off, washed with ethyl acetate and dried *in vacuo* to give 8.21 g. (63%) of a colourless crystalline solid.

Found:
C, 55.52; H, 4.82; N, 12.10; S, 5.97.
$C_{25}H_{23}O_6N_5SH_2O$ requires:
C, 55.62; H, 4.67; N, 12.97; 5, 5.94.

The ethyl acetate mother liquors were treated as described in Example 8 to give the penicillin sodium salt 2.42 g. (17.8%) as a colourless non-crystalline solid.

EXAMPLE 6.

D - α - (N - p - Iodobenzoylureido)benzylpenicillin.

A solution of p - iodobenzoyl isocyanate (6.53 g. 0.025 mol.) methylene chloride (30 ml.) was reacted with anhydrous D - α-aminobenzylpenicillin (8.73 g. 0.025 mol.) as described in Example 5 and the product isolated to give:—

(a) The penicillin free acid 4.65 g. (30.5%) as a colourless crystalline solid.

Found:
C, 46.37; H, 3.95; N, 8.64; S, 5.01.
I, 20.39.
$C_{24}H_{23}O_6N_4SI$ requires:
C, 46.31; H, 3.72; N, 9.00; S, 5.15;
I, 20.39.

(b) The penicillin sodium salt 5.64 g. (35.7%) as a colourless non-crystalline solid.

EXAMPLE 7.

D - α - (N - p - Phenylbenzoylureido)benzylpenicillin.

A solution of biphenyl 4-carbonyl isocyanate (5.58 g. 0.025 mol.) in methylene chloride (30 ml.) was reacted with anhydrous D-α-aminobenzoylpenicillin (8.73 g. 0.025 mol.) as described in Example 5 and the product isolated to give:

(a) The penicillin free acid 3.74 g. (26.2%) as a colourless crystalline solid.

Found:
C, 62.83; H, 5.08; N, 9.68; S, 5.94
$C_{30}H_{28}O_6N_4S$ requires:
C, 62.92; H, 4.93; N, 9.79; S, 5.60.

(b) The penicillin sodium salt 7.51 g. (50.6%) as a colourless non-crystalline solid.

EXAMPLE 8.

D - α - (N - 3,4 - Methylenedioxybenzoylureido)benzylpenicillin.

A solution of 3,4 - methylenedioxybenzoyl isocyanate (4.78 g. 0.025 mol.) in methylene chloride (30 ml.) was reacted with anhydrous D - α - aminobenzylpenicillin (8.73 g. 0.025 mol.) as described in Example 5 and the product isolated to give:—

(a) The penicillin free acid 9.34 g. (69.2%) as a colourless crystalline solid.

Found:
C, 55.40; H, 4.71; N, 9.71; S, 5.81.
$C_{31}H_{24}O_8N_4S$ requires:
C, 55.55; H, 4.48; N, 10.36; S, 5.93.

(b) The penicillin sodium salt 1.05 g. (7.5%) as a colourless non-crystalline solid.

EXAMPLE 9.

L - α - (N - Benzoylureido)benzylpenicillin.

A solution of benzoyl isocyanate (2.21 g. 0.015 mol.) in methylene chloride (10 ml.) was added, with stirring and cooling, to a clear solution of L - α - aminobenzylpenicillin (5.23 g. 0.015 mol.) in a mixture of methylene chloride (60 ml.) and triethylamine (4.5 ml.) at 0°C. The mixture was stirred at 0°C for 2 hours and worked up as described in Example 8 to give the penicillin sodium salt 5.63 g. (72.5%) as a colourless non-crystalline solid.

EXAMPLE 10.

α - (N - Benzoylureido)2 - thienylmethylpenicillin.

A solution of benzoyl isocyanate (2.21 g. 0.015 mol.) in methylene chloride (10 ml.) was added, with stirring and cooling to a clear solution of α - amino - 2 - thienylmethylpenicillin [epimer derived from α - amino-2 - thienylacetic acid $[\alpha]_D^{20}$ −74° (C=1, H_2O)] (5.32 g. 0.015 mol.) in a mixture of methylene chloride (75 ml.) and triethylamine (4.5 ml.) at 0°C. The mixture was stirred at 0°C for 2 hours and worked up as described in Example 8 to give the penicillin sodium salt 3.82 g. (48.6%) as a colourless non-crystalline solid.

EXAMPLE 11.

D - α - (N - Benzoylureido) - p - hydroxybenzylpenicillin.

D - α - Amino - p - hydroxybenzylpenicillin (1.46 g. 0.004 mol) in methylene chloride (20 ml.) was treated with triethylamine (1.2 ml.) and stirred for 20 minutes at room temperature. The solution was cooled to 0°C and a solution of benzoyl isocyanate (0.588 g. 0.004 mol.) in methylene chloride (12 ml) was added. After complete addition the mixture was stirred at 0°C for 2 hours. The methylene chloride was evaporated under reduced temperature and pressure and the residue dissolved in water (100 ml.). The aqueous solution was acidified to pH 1.5 with N hydrochloric acid in the presence of ethyl acetate (30 ml.). The organic layer was separated and the aqueous phase re-extracted with ethyl acetate (3 × 30 ml.). The combined ethyl acetate extracts were washed with water (10 ml.), dried over anhydrous magnesium sulphate and treated with a 1.67N solution of sodium 2-ethylhexoate in methyl isobutyl ketone (2.4 ml.). The resulting hazy solution was evaporated under reduced temperature and pressure and the residue triturated with dry ether to give 0.57 g. (27%) of the penicillin sodium salt as a colourless non-crystalline solid estimated to be 53.6% pure by colorimetric assay with hydroxylamine.

EXAMPLE 12.

D - α - (N - p - Toluenesulphonylureido)-benzylpenicillin.

Anhydrous D - α - aminobenzylpenicillin (3.49 g. 0.01 mol.) in methylene chloride (20 ml.) with triethylamine (3 ml.) was stirred at room temperature for 20 minutes and filtered through Celite. The clear filtrate, cooled to 0°C, was treated with stirring, with a solution of p-toluenesulphonylisocyanate (1.97 g. 0.01 mol.) in methylene chloride (10 ml.) and stirred at 0°C for 2 hours. The reaction solution was evaporated to dryness under reduced temperature and pressure and the residue dissolved in water (100 ml.). The aqueous solution was washed with ether (30 ml.) and acidified to pH 1.5 with N hydrochloric acid in the presence of ethyl acetate (30 ml.). The organic layer was separated and the aqueous layer re-extracted with ethyl acetate (2 × 30 ml.). The combined organic extracts were washed with water (10 ml.), dried over anhydrous magnesium sulphate, and treated with a 1.67N solution of sodium-2-ethylhexoate in methyl isobutyl ketone (6 ml.). The precipitated solid was filtered off, washed with dry ether and dried *in vacuo* to give 5 g. (88%) of the penicillin sodium salt as a colourless non-crystalline solid estimated to be 95.8% pure by colorimetric assay with hydroxylamine.

EXAMPLE 13.

D - α - (N - Benzenesulphonylureido)benzylpenicillin.

A solution of benzenesulphonyl isocyanate (4.57 g. 0.025 mol.) in methylene chloride (30 ml.) was added with stirring and cooling to a clear solution of anhydrous D - α - aminobenzylpenicillin (8.73 g. 0.025 mol.) in a mixture of methylene chloride (50 ml.) and triethylamine (7.5 ml.) at 0°C. The reaction mixture was stirred at 0°C for 2 hours and worked up as described in Example 12 to give 10.73 g. (77.4%) of the penicillin sodium salt as a colourless non-crystalline solid estimated to be 99% pure by colorimetric assay with hydroxylamine.

EXAMPLE 14.

D - α - (N - p - Chlorobenzenesulphonylureido)benzylpenicillin.

A solution of p-chlorobenzenesulphonyl isocyanate (3.87 g. 0.0178 mol.) in methylene chloride (20 ml.) was added with stirring and cooling, to a clear solution of D - α-aminobenzylpenicillin (6.21 g. 0.178 mol.) in a mixture of methylene chloride (36 ml.) and triethylamine (5.4 ml.) at 0°C. The reaction mixture was stirred at 0°C for 2 hours and worked up as described in Example 12 to give 6.49 g. (61.8%) of the penicillin sodium salt as a colourless non-crystalline solid estimated to be 93% pure by a colorimetric assay with hydroxylamine.

EXAMPLE 15.

D - α - (N - Methanesulphonylureido)benzylpenicillin.

A solution of methanesulphonyl isocyanate (3.4 g. 0.028 mol.) in methylene chloride (15 ml.) was added with stirring and cooling, to a clear solution of anhydrous D - α - aminobenzylpenicillin (9.77 g. 0.028 mol.) in a mixture of methylene chloride (110 ml.) and triethylamine (8.6 ml.) at 0°C. The mixture was stirred at 0°C for 2 hours and worked up as described in Example 12 to give the penicillin sodium salt 10.24 g. (75.9%) as a colourless non-crystalline solid.

EXAMPLE 16.

D - α - (N - p - Nitrobenzenesulphonylureido)benzylpenicillin.

A solution of p-nitrobenzenesulphonyl isocyanate (6.2 g. 0.027 mol.) in methylene chloride (15 ml.) was added, with stirring and cooling, to a clear solution of anhydrous D-α-aminobenzylpenicillin (9.5 g. 0.027 mol.) in a mixture of methylene chloride (110 ml.) and triethylamine (8.4 ml). at 0°C. The mixture was stirred at 0°C. for 2 hours and worked up as described in Example 23 to give the penicillin sodium salt 12.7 g. (78.8%) as a pale yellow non-crystalline solid.

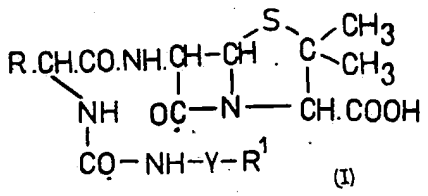
The following Table illustrates the *in vitro* antibacterial activity (expressed as Minimum Inhibitory Concentrations in mcg./ml.) of the penicillins of the present invention against a selection of Gram-positive and Gram-negative bacteria. The Table includes figures for penicillin G, ampicillin and carbenicillin for comparison purposes and shows that the penicillins of the present invention have an exceptionally broad spectrum of antibacterial activity.

Penicillin	Staph. Oxford	Strep. Faecalis	Strep. pneumoniae	E. coli	Salm. typhi	Shigella flexneri	Proteus mirabilis	Proteus morganii	Pseudomonas pyocyanea
Penicillin G	0.02	2.5	0.02	25	2.5	12.5	5	500	>500
Ampicillin	0.05	1.25	0.1	2.5	0.25	1.25	1.25	62.5	>250
Carbenicillin	1.25	125	2.5	5	5	12.5	12.5	5	50
Compound of Example No.									
1	0.1	1.25	0.02	12.5	12.5	5	5	12.5	12.5
2	0.25	1.25	0.01	5	5	2.5	1.25	5	12.5
3	0.01	1.25	0.01	5	5	5	25	5	12.5
11	0.5	2.5	0.02	25	25	12.5	12.5	25	25
12	1.25	25	–	25	25	25	2.5	50	50
13	0.5	25	0.12	25	25	12.5	0.5	125	50
14	0.5	12.5	0.02	12.5	12.5	12.5	0.5	–	50
15	2.5	25	0.5	12.5	12.5	12.5	0.5	500	>500
16	2.5	12.5	0.5	50	50	25	5	250	500
4a	0.5	1.25	0.01	12.5	12.5	12.5	5	12.5	12.5
4b	0.12	1.25	0.01	12.5	12.5	5	5	12.5	12.5
4c	0.25	1.25	–	5	5	5	2.5	12.5	12.5
4d	0.5	2.5	–	50	25	25	12.5	500	25

Penicillin	Staph. Oxford	Strep. faecalis	Strep. pneumoniae	E. coli	Salm. typhi.	Shigella flexneri	Proteus mirabilis	Proteus morganii	Pseudomonas pyocyanea
4e	0.25	2.5	–	12.5	12.5	12.5	12.5	12.5	25
4f	0.5	2.5	–	25	25	12.5	12.5	25	50
4g	0.12	12.5	–	25	25	12.5	12.5	25	25
4h	–	5	<0.01	5	12.5	5	5	5	12.5
4i	0.1	2.5	0.02	12.5	12.5	12.5	2.5	12.5	50
4j	0.5	2.5	0.05	25	25	12.5	5	25	50
4k	0.25	1.25	<0.01	5	5	2.5	2.5	2.5	12.5
4l	0.5	50	0.1	12.5	2.5	50	1.25	250	>500
4m	0.25	2.5	0.02	25	25	12.5	5	12.5	125
4n	1.25	1.25	<0.01	25	5	5	50	12.5	25
4p	0.5	2.5	0.02	25	5	12.5	2.5	125	12.5
4q	0.25	1.25	0.05	25	12.5	12.5	12.5	25	25
4r	1.25	12.5	0.12	12.5	12.5	12.5	2.5	250	250
4s	1.25	5	<0.01	50	25	25	25	125	125
4t	0.25	1.25	<0.01	12.5	5	5	12.5	12.5	5
4u	0.12	1.25	<0.01	12.5	5	5	2.5	25	12.5
4v	0.5	5	0.1	25	50	25	25	250	250
5	0.25	2.5	0.02	25	12.5	12.5	2.5	12.5	25
6	0.12	1.25	<0.01	12.5	12.5	5	5	25	25
7	0.05	0.5	<0.01	5	5	2.5	2.5	12.5	25
8	0.1	–	<0.01	12.5	12.5	5	25	25	12.5
9	0.5	5	0.1	>500	>500	500	500	>500	>500
10	0.1	1.25	<0.01	25	12.5	12.5	5	12.5	25

WHAT WE CLAIM IS:—

1. Penicillins of the general formula (I):—



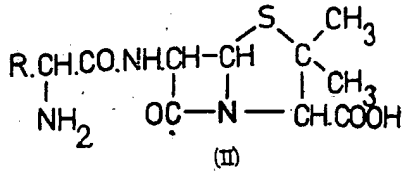
(I)

and non-toxic salts thereof, where R is a phenyl, substituted phenyl or thienyl group, R^1 is an alkyl, alkenyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, alkylthio, arylthio, aralkylthio or heterocyclic group which may be substituted and Y is SO_2.

2. Penicillins of the general formula (I) and non-toxic salts thereof in which R is a phenyl or thienyl group, R^1 is as defined in claim 1, but Y is the group CO.

3. Penicillins as claimed in claim 2 wherein R^1 is a 2-furyl or methyl group.

4. A process for the preparation of the penicillins and non-toxic salts thereof which process comprises reacting in an organic solvent an α-aminopenicillin of the general formula (II):—



(II)

or a salt thereof with an isocyanate of the general formula $R^1 . Y . NCO$ where R, R^1 and Y have the meanings given in claim 1.

5. A process for the preparation of penicillins and non-toxic salts thereof which process comprises reacting in an organic solvent an α-aminopenicillin of the general formula (II) or a salt thereof with in isocyanate of the general formula $R' . Y . NCO$ where R, R^1 and Y have the meanings given in claim 2.

6. A process as claimed in claim 5 wherein R^1 has the meaning given in claim 3.

7. A process as claimed in claim 5 wherein the α - aminopenicillin is D - α - aminobenzylpenicillin.

8. A process for the preparation of penicillins and non-toxic salts thereof as claimed in claim 2 substantially as described with reference to any one of the Examples 1, 2, 3, 4a and 4d.

9. Penicillins and non-toxic salts thereof as claimed in claim 2 when prepared by the process claimed in any one of claims 5 to 8.

10. Penicillins of the general formula (I) and non-toxic salts thereof in which R is a phenyl group, Y is CO and R^1 is an optionally substituted alkyl, alkenyl, aryl, aralkyl or heterocyclic group.

11. A penicillin as in claim 10 wherein R^1 is a CH_3 group.

12. A penicillin as in claim 10 wherein R^1 is a p-methoxyphenyl group.

13. A penicillin as in claim 10 wherein R^1 is a 2-furyl group.

14. A penicillin as in claim 10 wherein R^1 is a 3-thienyl group.

15. A penicillin as in claim 10 wherein R^1 is a p-benzyloxyphenyl group.

16. A penicillin as in claim 10 wherein R^1 is an *iso*-valeryl group.

17. A penicillin as in claim 10 wherein R^1 is a phenyl group.

18. A penicillin as in claim 10 wherein R^1 is a p-chlorophenyl group.

19. A penicillin as in claim 10 wherein R^1 is a 2-thienyl group.

20. A penicillin as in claim 10 wherein R^1 is a *n*-propyl group.

21. A penicillin as in claim 10 wherein R^1 is an *o*-methoxyphenyl group.

22. A penicillin as in claim 10 wherein R^1 is a *m*-methoxyphenyl group.

23. A penicillin as in claim 10 wherein R^1 is a *p*-chlorophenyloxymethyl group.

24. A penicillin as in claim 10 wherein R^1 is a benzyl group.

25. A penicillin as in claim 10 wherein R^1 is a p-bromophenyl group.

26. A penicillin as in claim 10 wherein R^1 is a trichloromethyl group.

27. A penicillin as in claim 10 wherein R^1 is a *p*-nitrophenyl group.

28. A penicillin as in claim 10 wherein R^1 is a *p* - $(C_6H_5CH_2OOCNH)C_6H_4$. group.

29. A penicillin as in claim 10 wherein R^1 is a *p*-fluorophenyl group.

30. A penicillin as in claim 10 wherein R^1 is a 2,6 - dimethoxyphenyl group.

31. A penicillin as in claim 10 wherein R^1 is a *p*-cyanophenyl group.

32. A penicillin as in claim 10 wherein R^1 is a *p*-iodophenyl group.

33. A penicillin as in claim 10 wherein R^1 is a p-phenylphenyl group.

34. A penicillin as in claim 10 wherein R^1 is a 3,4-methylenedioxyphenyl group.

35. Penicillins of the general formula (I) and non-toxic salts thereof in which R is a phenyl group, Y is CO and R^1 is a group OR'' wherein R'' is an optionally substituted alkyl, aryl, or aralkyl group.

36. A penicillin as in claim 35 wherein R'' is a benzyl group.

37. A penicillin as in claim 35 wherein R'' is an ethyl group.

38. A penicillin as in claim 35 wherein R'' is a phenyl group.

39. L - α - (N - Benzoylureido)benzylpenicillin.

40. α - (N - Benzoylureido) - 2 - thienylmethylpenicillin.

41. D - α - (N - Benzoylureido) - p - hydroxybenzylpenicillin.

42. D - α - (N - p - Toluenesulphonylureido)benzylpenicillin.

43. D - α - (N - Benzenesulphonyl ureido)-benzylpenicillin.

44. D - α - (N - p - Chlorobenzenesulphonylureido)benzylpenicillin.

45. D - α - (N - Methanesulphonylureido)-benzylpenicillin.

46. D - α - (N - p - Nitrobenzenesulphonylureido)benzylpenicillin.

RONALD SMITHER,
Agent for the Applicants,
Chartered Patent Agent.

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